REMARKS

Applicants respectfully submit this Supplemental Reply under the assumption that the amendments presented in the Amendment filed on May 13, 2008 have been entered. By the present communication, claims 1, 3, 22, 51, and 56 have been amended. Claim 59 is added. No new matter is introduced by way of amendment. Support for the amendments may be found throughout the application as originally filed, including, but not limited to, original claim 3 and p. 10, line 4 to p. 11 line 12. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Claim Rejections, 35 U.S.C. § 103(a) – Paweletz in view of Bishop

In the Office Action, claims 51-55 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Paweletz *et al.* (2001 *Oncogene* 20: 1981-1989) in view of Bishop (U.S. Patent No. 6,316,462). Applicants traverse this rejection for the reasons given in the Amendment filed on May 13, 2008. Applicants provide the following additional remarks with regard to the non-obviousness of the instant claims over the combination of Paweletz and Bishop.

A. Protein signaling defects in diseased cells exhibit unexpected heterogeneity in individual patients, which provides a rational basis for personalized medicine.

The methods of the instant claims are based on the surprising discovery that the activity states of cell signaling proteins vary from individual to individual, even if those individuals suffer from the same medical condition. The present inventors measured the activity state of many proteins in cell lysates from *individual patients* and found striking differences in the activity states of interconnected signaling pathways. (*See* Specification, p. 75, line 23 to p. 77, line 4). This result was unexpected and could not be predicted by measuring the mRNA levels using nucleic acid microarrays (Specification, p. 77, lines 3-4).

Because the differences in protein signaling networks differ among patients with the same medical condition, it becomes important to select the appropriate combination of agents for the medical condition affecting the individual. A particular combination of therapeutic agents may

be beneficial for the treatment of a medical condition in some individuals, but disastrous (or at the very least ineffective) for the treatment of the same medical condition in other individuals. Since the filing date of the instant application, several studies by the present inventors have demonstrated the power of these methods to evaluate the changes in a patient's signaling network as a rational underpinning for selecting a combination therapy for that patient. *See* enclosed declaration under 37 C.F.R. § 1.132 by Dr. Lance A. Liotta ("Liotta Declaration").

Using the reverse phase protein microarray technology described in the instant application, the inventors and their colleagues measured the activity states of a plurality of different signaling proteins extracted from diseased cells of individual patients suffering from metastatic ovarian carcinoma. The data revealed a large degree of heterogeneity within each patient. *See* Liotta Declaration, ¶ 6. The activity states of signaling proteins were also dramatically changed in tumor metastases compared to the matched primary tumors within the same individual. Based on the observed signaling differences, the authors concluded that many patients may benefit from Gleevec therapy (a tyrosine kinase inhibitor) in combination with other kinase inhibitors that could be determined from that patient's particular phosphoproteomic fingerprint (Liotta Declaration, ¶ 9). These results indicate specific combinations of therapeutic agents that are tailored to the individual may be used to target disseminated cells.

In a study of breast cancers, reverse-phase protein microarray technology was shown to be a useful platform to elucidate the complex cellular signaling derangements that underpin each patient's tumor, and helped distinguish between patients who might benefit from one type of therapy or another (Liotta Declaration, ¶ 49). The conclusion of this study was that the identification, characterization, and monitoring of signaling events within actual human biopsies is an essential step in the patient-tailored diagnostic-therapeutic regime of breast cancer. Measuring the activity states for a plurality of different signaling proteins is necessary for the precise characterization of pathways for the proper selection of combinations of therapeutic agents to treat individual subjects. (Liotta Declaration, ¶¶ 49-50). Thus, these experiments further illustrate the utility of the instant methods to identify signaling defects in diseased cells as

a rational basis for selecting a patient-tailored therapy. Similar results were obtained in studies of follicular lymphoma (Liotta Declaration, ¶¶ 10-17) and childhood rhabdomyosarcoma (Liotta Declaration, ¶¶ 18-39).

The instant methods also include selecting individualized therapies for diseases and medical conditions other than cancer. For example, one study found cell signaling defects that differentiated between progressive and non-progressive forms of Nonalcoholic Fatty Liver Disease (NAFLD) (Liotta Declaration, ¶¶ 29-31). Using the reverse phase protein microarray ments described in the instant application, the activity states for a plurality of different signaling proteins were studied in white adipose tissue from patients with different subtypes of NAFLD (Liotta Declaration, ¶ 32). The investigators found changes in pathways related to insulin resistance, as well as the PKC lipolysis pathway, and the AKC/mTOR pro-survival/apoptosis pathways (Liotta Declaration, ¶ 34). These findings identified potential targets for the selection of combinations of therapeutic agents for a subject suffering from NAFLD, wherein the agents are capable of reducing the differences in the detected activity states (Liotta Declaration, ¶ 34-35).

Likewise, heterogeneity in protein signaling pathways was observed in patients suffering from wet age-related macular degeneration, which may provide a basis for individualized therapy (Liotta Declaration, ¶ 51). Using the reverse phase protein microarray methods described in the instant application, the activity states for a plurality of different signaling proteins were studied in the vitreous fluid from individual patients suffering from wet age-related macular degeneration with the goal of identifying candidate therapeutic targets. The researchers identified signaling proteins related to neovascularization, apoptosis, oxidative stress, adhesion, glucose/insulin metabolism and inflammation (Liotta Declaration, ¶ 51). In particular, significant differences in the activity states of different signaling pathways were observed among patients with wet age-related macular degeneration. These data provide new therapeutic targets for a disease that has been refractory to treatment.

Taken together, these post-filing date studies, based on the methods and inventions described in the application specification, demonstrate the remarkable utility of the instant methods to identify particular protein signaling defects in diseased cells isolated from an individual in order to select an appropriate combination therapy for the individual. The efficacy of the methods for personalized medicine could not have been predicted based from the prior art.

B. Paweletz and Bishop fail to teach or suggest that measuring protein signaling defects in diseased cells could provide a basis for individualized combinatorial therapy.

The amended claims are directed to selecting an effective treatment for *an individual subject* suffering from a variety of pathological conditions that relate to aberrant protein signaling. Neither Paweletz nor Bishop teaches or suggests the power of the these methods to reveal individual differences in disease networks that are critical to proper treatment of disease. In particular, Bishop suggests treating patients having all types of cancer with the same combination of drugs: a farnesyl protein transferase (FPT) inhibitor and an additional Ras signaling pathway inhibitor. (Bishop, col. 2, lines 41-45.) Bishop states that their methods are "useful for the treatment of various tumorigenic cancers, especially epithelial cancer, (e.g., pancreatic cancer, ovarian cancer, prostate cancer, lung cancer, breast cancer, colorectal cancer, and bladder cancer), and melanoma." (Bishop, col. 2, lines 63 to 67). Thus, Bishop failed to recognize that particular cancers—*let alone particular individuals*—might possess differences is the activity states of cell signaling networks that would require individualized therapy.

The deficiencies of Bishop are also lacking from Paweletz. Paweletz does not teach or suggest measuring the activity states of cell signaling networks in individual subjects and selecting a treatment regime based on observed differences. Moreover, the combination of Paweletz and Bishop fails to support a finding of obviousness because one of skill in the art would not have combined the references with a reasonable expectation of success. The Office Action states:

> One of ordinary skill in the art would have had a reasonable expectation of success in combining the reverse phase protein

> microarray based analysis of phosphorylation states of Paweletz et al to select farnesyl transferase inhibitors [and] additional Ras signaling pathway inhibitors per Bishop et [al] because both analyze Erk and caspase activity, thus the drug candidates of Bishop are directed to the same proteins and/or pathways that concern Paweletz et al.
> (Office Action, p. 14).

Applicants respectfully disagree. The teachings of Paweletz and Bishop are contradictory and teach away from the idea of using a farnesyl transferase inhibitor and an additional Ras signaling pathway inhibitor in the treatment of disease for individual patients. Paweletz teaches that decreased phosphorylation of ERK was positively correlated with cancer progression in prostate cancer (Paweletz, p. 1985, right column.) In particular, Paweletz found that phosphorylated ERK is suppressed during the progression of prostate cancer, with normal epithelium expressing the highest level of ERK with a gradual decline as the disease progresses. (*Id.*) These data would lead one of skill in the art to conclude that a treatment regime for prostate cancer could include an agent that *increases* phosphorylation of ERK.

To the contrary, Bishop showed that the combination of the FPT inhibitor SCH 55335 and MEK inhibitor PD098059 *decreased* the phosphorylation of ERK1 and ERK2 in Ras-transformed fibroblasts (col. 44, lines 35 to 52). This result is at odds with the findings of Paweletz. If one of skill in the art wished to select a combination of therapeutic agents that reduced the difference in activity states between normal and diseased prostate cancer cells, they would not select a farnesyl transferase inhibitor and an additional Ras signaling pathway inhibitor as in Bishop. Because the agents administered by Bishop produced exactly the opposite effect one would wish to induce based on the teachings of Paweletz, one of skill in the art would not have combined the references with a reasonable expectation of success. As such, a *prima facie* case of obviousness cannot be established. Applicants respectfully request withdrawal of this rejection.

II. Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. If any matters remain open after consideration of this response, the Examiner is invited to contact the undersigned by telephone at the number set forth below so that a prompt disposition of the application can be achieved.

Respectfully submitted,

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